with the soluble TNF-α receptor etanercept. However, researchers in Chicago report that four female patients developed symptoms of SLE during treatment with etanercept, highlighting the need for caution in the use of this drug and the need to clarify the prevalence and pathogenesis of the these responses (*The Lancet* 359, 579–580). *SW*

CD40 ligand sheds LIGHT on graft-versus-host disease

Graft-versus-host disease (GVHD) is caused by alloreactive immune responses and is a major complication of bone marrow transplantation. Pharmacological agents with immunosuppressive actions prevail as major therapeutic interventions, but they require prolonged administration that can result in general immune suppression. Previous studies have shown that blockade of the T cell costimulatory molecule LIGHT by soluble lymphotoxin receptor-Ig (LTR-Ig) ameliorates lethal GVHD in a mouse model. Researchers at the Mayo Clinic in the USA now report that infusion of a monoclonal antibody against CD40 ligand further increases the efficacy of LTR-Ig, leading to complete prevention of GVHD. Alloantigen-specific cytotoxic T-lymphocytes become anergic and persist in the tolerized mice as a result of costimulatory blockade and tranfer of anergic CTLs to recipient mice fails to induce GVHD. The study provides a potential new and exciting approach for the prevention of lethal GVHD (*J. Clin. Invest.* 109, 549–557). *SW*

One AIDS battle over

Although the fight against AIDS is still raging, at least one battle has ended with the announcement in February that the researchers Robert Gallo and Luc Montagnier are to collaborate on developing AIDS vaccines for Africa. The two plan to merge their vaccine approaches more than almost two decades after their famous falling-out over accreditation for the discovery of HIV and the resultant blood test. Gallo's team focuses on tacking various HIV genes into *Salmonella*, whereas Montagnier concentrates on making vaccines from HIV proteins gag, tat and nef. Montagnier, who now heads the World Foundation for AIDS Research and Prevention cites one reason for the collaboration: 'If we join our efforts, it will be more credible for fund-raising.' Testing of Gallo's vaccines could be speeded up by tapping into data produced from Montagnier's recent testing sites in Côte d'Ivoire and Cameroon. However, within the HIV research community, there is doubt as to the substance of potential collaborations, because Montagnier, for example, still contends that HIV relies on cofactors to cause disease, an idea that Gallo contends. Stay tuned for developments in this high-profile relationship (*Science* 295, 1441–1442). *AL*

Can cytokines shrink babies?

Growth *in utero* has a profound effect on the expression of genetic potential. Its retardation can impede neurological development and is associated with higher neonatal death rates, early onset diabetes and cardiac disease. Levels of placental cytokines have been found to relate to birth weight in groups of Swedish infants. PCR analysis of placentae collected from groups of infants showed a reduction in the IL-10 mRNA in situations of intrautine growth retardation, without any of the cytokine changes suggestive of hypoxia or inflammation, which are other causes of growth retardation. It is possible that this is a primary event, resulting in a bias towards Th1 cytokine production. This in turn might lead to inadequate placental support and diminished growth of the fetus (*Ped. Res.* 51, 201–206). *CM*

Tolls for viruses

Of the ten members of the toll-like receptor (TLR) family, ligands have been identified for only six. Several TLRs, including TLR7, do not have clearly described roles. Investigation into the antiviral imidazoquines have shown that they activate the immune system as a crucial part of their activity. Mice defective in TLR7 expression, or in the signalling components used by TLRs, do not show either immune activation or antiviral activities when exposed to these compounds, suggesting a link between TLR7 and viral defences. The exact ligands involved need to be determined, as do the connections between TLR7 and interferon-α production. Therapeutically, this offers new vistas for antiviral adjuvants that can exploit TLRs; imidazoquines could become pioneering compounds that are crucial to improved vaccination programs (*Nat. Immunol.* 3, 196–200). *CM*

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Letter

Immunoneutralization and anti-idiotype production: two-sided applications of leptin

The neuroendocrine and immune systems are linked through a complex bi-directional network, in which hormones modify immune function, and the immune system, through the action of cytokines, affects neuroendocrine responses involved in the maintenance of body homeostasis. The adipocyte-derived, peptide hormone leptin is a pleiotropic molecule belonging to the helical cytokine family. On pp. 182–187, Matarese *et al.* suggest the possibility of new leptin-based therapeutic strategies for the treatment of both infection and autoimmune disease.

It is believed generally that the primary physiological function of leptin is to coordinate metabolic, endocrine and behavioral responses to changing energy status. The level of secreted leptin is proportional to body-fat level [1], and through its actions on hypothalamic centers, leptin suppresses food intake and increases energy expenditure. Besides its actions on appetite and metabolism, leptin is capable of modulating the immune response also. Functional leptin receptors are found on human monocytes [2] and exogenous leptin has been found to up-regulate macrophage phagocytosis and the production of proinflammatory cytokines [3], as well as enhance T-helper-cell responses [4].

The production of leptin is influenced by nutritional status, with malnutrition or

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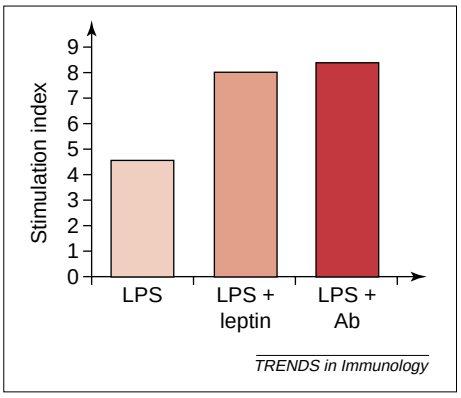

Fig. 1. Anti-idiotype antibody (Ab) mimics the enhancing effect of leptin on lymphocyte proliferation. The proliferative response of lymphocytes isolated from spleen was determined using the [^{3}H]-thymidine method after 72 hours of culture in RPMI culture medium with lipopolysaccharide (LPS) from *Escherichia coli* (50 μg ml^{-1}), LPS plus leptin (1.7 μg ml^{-1}) or LPS plus anti-idiotype antibody (1.7 μg ml^{-1}). The addition of leptin or anti-idiotype antibody to LPS led to a 75% or 83% increase in lymphocyte proliferation, respectively. A nonparametric Friedman's test was used (P<0.05; n = 6) to analyze the data.

starvation resulting in both reduced circulating leptin levels and suppressed immune function. Animals with a deficiency in the ability to produce leptin [5] or genetic defects in the leptin receptor [6] are markedly hyperphagic and obese, and have impaired cell-mediated immunity [7]. The administration of exogenous leptin reduces hyperphagia, induces weight loss [8] and reverses starvation-induced immunosuppression [4]. By contrast, too much leptin seems to increase susceptibility to autoimmune reactions. Female mice, which have elevated leptin levels compared with males, are more susceptible to disease in autoimmune models, whereas leptin treatment reverses male resistance to autoimmune diseases [9].

Perhaps, leptin-based immunotherapy could be used in synergy with other strategies to treat both infection and autoimmune disease. That is, antileptin therapies might reduce or block the activation and priming of pathogenic T-cell populations in autoimmune diseases [9], whereas leptin agonists could be used to augment the immune system and reduce susceptibility to infection in undernourished and immunosuppressed individuals. A novel proposal is the use and/or induction of expression of antibodies to either immunoneutralize or serve as surrogate ligands. Antibodies can reduce circulating hormone levels, thereby reducing some *in vivo* functions [10], whereas anti-idiotype antibodies, carrying an 'internal image' of an epitope of the external antigen (i.e. leptin) [11], have the potential to transduce signals upon binding to their receptors. A leptin anti-idiotype antibody can reproduce the potentiating effects of leptin on lymphocyte proliferation (Fig. 1), as well as mimic leptin's central effects on food intake and thermogenesis [12].

Alterations in the leptin-mediated immune–neuroendocrine homeostatic network result in pathophysiological conditions, suggesting an immunomodulatory role for leptin in susceptibility to infection and autoimmunity (see pp. 182–187). The demonstration that immunization with a monoclonal anti-leptin antibody reduces leptin biological activity (Fig. 2a), whereas leptin anti-idiotypes exert some of the same *in vivo* effects as leptin (Fig. 2b), suggests that immunomanipulation might be a promising approach to reducing susceptibility to infection and autoimmunity, as well as regulating body-weight homeostasis. With the number of undernourished people in the world remaining high and an estimated quarter of all obese people being leptin-deficient [13], the effects of leptin on immunocompetence proposed by Matarese *et al.* suggest that a very large population could benefit potentially from leptin therapy, and humanized antibodies might be potential therapeutic agents for several leptin-related disorders.

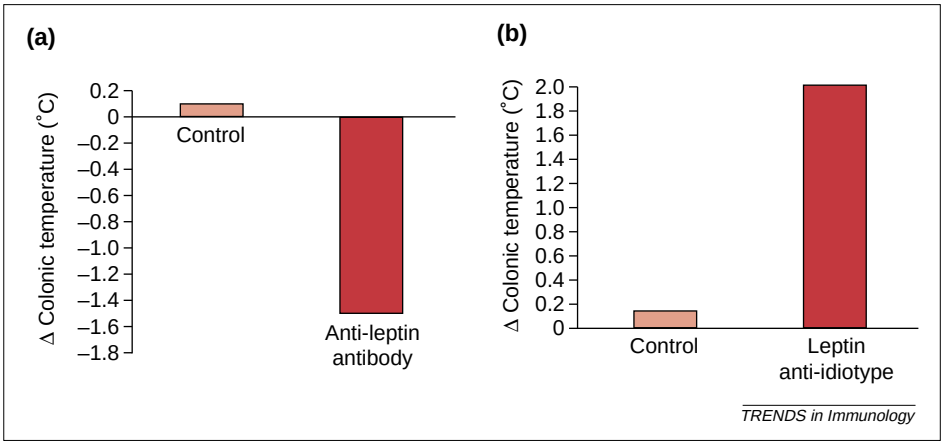

Fig. 2. Acute changes in colonic temperature after (a) intravenous anti-leptin antibody administration in mice [10] or (b) intracerebroventricular administration of anti-idiotype in rats [12].

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